Br. J. clin Pharmac. (1985), **19**, 211–217

Pharmacokinetics of ornidazole in patients with renal insufficiency; influence of haemodialysis and peritoneal dialysis

H. MERDJAN[1], A. BAUMELOU[2], B. DIQUET[1], O. CHICK[2] & E. SINGLAS[1]
[1]Service de Pharmacie Clinique, Hôpital Bicêtre, Le Kremlin Bicetre, France and [2]Service de Néphrologie (Pr. M. Legrain), Hôpital Pitié-Salpétrière, Paris, France

1 The pharmacokinetics of ornidazole (Tiberal®) was studied after intravenous administration of a single 500 mg dose in eight patients with advanced chronic renal failure (ACRF) (creatinine clearance 2–16 ml/min), in seven patients treated by haemodialysis (residual renal creatinine clearance 0–5 ml/min) and in five patients treated by continuous ambulatory peritoneal dialysis (CAPD) (residual renal creatinine clearance 0–6 ml/min).

2 In ACRF patients, the half-life of ornidazole was 10.8 ± 1.4 h, the total plasma clearance 46.3 ± 2.3 ml/min and the volume of distribution 0.73 ± 0.06 l/kg.

3 During haemodialysis, ornidazole was partly removed: the dialyser extraction ratio was 42 ± 5% and the dialysis clearance 64 ± 7 ml/min.

4 During CAPD, peritoneal excretion was low: the dialysis clearance was 3.0 ± 0.4 ml/min and in 48 h 6.0 ± 1.1% of the administered dose was found in the peritoneal fluids. In these patients, the half-life of ornidazole was 11.8 ± 0.8 h and total plasma clearance was 48.3 ± 5.5 ml/min, values which were close to those determined in non dialysed patients.

5 In patients with end-stage renal disease, the half-life of ornidazole is comparable to that of subjects with normal renal function. This is due to the predominantly extra-renal elimination of the drug. Therefore, there is no need to modify the usual dosage of ornidazole for these patients. Because of the large elimination of the drug during haemodialysis it is necessary to administer the drug after the dialysis session.

Keywords ornidazole pharmacokinetics haemodialysis peritoneal dialysis

Introduction

Ornidazole-[α-(chloromethyl)-2 methyl -5 nitroimidazole -1-ethanol] (Tiberal®, Roche Laboratories) is a nitro-imidazole derivative with antiprotozoal and antibacterial properties; it is used for this latter property in the prevention and treatment of infections with anaerobic germs, such as *Bacteroides fragilis* (Goldstein *et al.*, 1978; Jokipii & Jokipii, 1977; Richle *et al.*, 1978). The drug is especially useful in abdominal or gynaecological surgery.

Pharmacokinetic data have not been reported for patients with severe renal failure; likewise no data are available on the effect of various dialysis techniques on the elimination of this drug.

Since renal insufficiency patients, dialysed or not, have been shown to be inordinately susceptible to bacterial infections, ornidazole would probably be used in these patients if the effect of renal insufficiency and dialysis on the pharmacokinetics of the drug is known and if proper dosage schedules could be devised.

Our study was designed to characterize ornidazole kinetics and to provide a basis for appropriate dosage adjustments in case of severe renal failure, during haemodialysis and continuous ambulatory peritoneal dialysis.

Correspondence: Dr E. Singlas, Pharmacie, Hôpital Bicêtre, 78, rue du Général Leclerc, 94270 Le Kremlin Bicetre, France

Methods

Patients

Seventeen patients with advanced chronic renal failure (ACRF) (creatinine clearance under 16 ml/min), whether treated by dialysis or not, were studied after obtaining their informed consent. Patients 1, 6 and 8 were investigated twice. The patient's characteristics are summarized in Table 1.

The patients were divided into three groups:

Group 1: Eight patients (nos 1 to 8), six men and two women were studied in the absence of dialysis. They were 25 to 70 years old (mean 47 years), their weight ranged from 42 to 81 kg (mean 60 kg) and their creatinine clearance was between 1.8 and 15.6 ml/min (mean 8.8 ml/min). Although patients 6 and 8 were treated by haemodialysis, a first investigation was performed during the 48 h interdialytic period.

Group 2: Five patients (nos 9 to 13), four men and one woman, were studied undergoing continuous ambulatory peritoneal dialysis (CAPD). They were 25 to 82 years old (mean 50 years) and their weight ranged from 52 to 70 kg (mean 61 kg). The residual renal creatinine clearance was between 0.0 and 6.0 ml/min (mean 2.7 ml/min) and peritoneal creatinine clearance between 4.2 and 6.0 ml/min (mean 4.8 ml/min). When investigated the five patients were free of peritonitis.

CAPD was performed according to the technique proposed by Oreopoulos *et al.*, (1978) using a previously described method (Renaux *et al.*, 1980). Five 2 l plastic bags were used each day.

Group 3: Seven male patients (nos 14 to 17 and patients 1, 6 and 8 from group 1 in a second investigation) were studied during haemodialysis. They were 27 to 67 years old (mean 49 years), their weight ranged from 54 to 71 kg (mean 63 kg) and their residual renal creatinine clearance was between 0.0 and 5.4 ml/min (mean 1.7 ml/min). Haemodialysis (4 h) was performed with a double needle access in arteriovenous fistulas, using a cuprophan membrane dialyser (CF 1511, Travenol Laboratories). The dialysate flow rate was 500 ml/min. Patient no 1 was studied twice: a first time while not yet under haemodialysis (creatinine clearance 9 ml/min) and 2 months later a second time with the group of haemodialysed patients as his renal function had worsened (creatinine clearance 3 ml/min).

Experimental design

The 17 patients were given, over 2 to 4 min, a

Table 1 Patient characteristics

Patient	*Sex*	*Age (years)*	*Weight (kg)*	*Creatinine clearance (ml/min)* *Renal*	*Peritoneal*	*Renal disease*
1	M	67	63	9.0(3.0*)		NAS
2	F	70	81	9.6		UN
3	M	32	48	15.6		PN
4	M	25	42	6.0		PN
5	F	51	54	11.4		PKD
6	M	42	62	1.8		PN
7	M	41	68	12.0		UN
8	M	51	65	5.4		NAS
9	M	25	70	6.0	4.3	CGN
10	M	82	57	5.4	4.2	PN
11	M	32	52	0.0	6.0	UN
12	M	40	65	0.0	5.0	NAS
13	F	69	61	2.0	4.6	PN
14	M	43	62	0.0		DN
15	M	53	64	0.0		PN
16	M	27	54	1.6		UN
17	M	64	71	0.0		CGN

(* creatinine clearance during the second study in haemodialysis, 2 months after the first study without dialysis)

NAS: nephroangiosclerosis, UN: unknown nephropathy, PN: pyelonephritis, PKD: polycystic kidney disease, CGN: chronic glomerulonephritis, DN: diabetic nephropathy

single intravenous dose of 500 mg ornidazole into a forearm vein. Venous blood samples (5 ml on dry heparin) were obtained at time 0, 0.5, 1, 2, 4, 10, 24 and 48 h after ornidazole injection from patients of groups 1 and 2.

For the patients in group 3, ornidazole was injected at the start of dialysis and arterial blood samples entering the dialyser (5 ml on dry heparin) were obtained during the haemodialysis session at time 0, 0.5, 1, 2, 2.5 and 4 h after drug injection. At 2.5 h a sample was also obtained in venous blood leaving the dialyser for calculating the haemodialysis clearance. The dialyser blood flow was measured by bubble transit time at 0, 1.5 and 3 h. The blood flow used in the clearance calculations was the mean value of the three determinations.

Blood samples were immediately centrifuged and the plasma separated and stored at –30° C until assayed.

For the patients of group 2 (CAPD), all dialysate bags were collected for the duration of the study, the volume was measured and aliquots were frozen at –30° C for assay.

Ornidazole assay

Plasma and peritoneal ornidazole concentrations were determined by reverse phase high performance liquid chromatography according to the method proposed by Merdjan *et al.* (1983). The detection limit was 0.2 mg/l.

Ornidazole was found to be stable in peritoneal dialysate, and no adsorption occurred onto the plastic of the dialysis bag.

Pharmacokinetic analysis

Data were analyzed by model independent methods.

The terminal phase rate constant (λ_z) was determined as the slope of the terminal monoexponential decline in plasma concentration/time by the least-square method. The terminal plasma half-life ($t_{1/2}$) was calculated by the equation $t_{1/2} = 0.693/\lambda_z$. The area under the plasma concentration time curve (AUC) was calculated by the trapezoidal rule from time 0 to time t of the last sample and extrapolated to infinity according to the formula $AUC_{t\infty} = C_t/\lambda_z$ where C_t is the plasma concentration of the drug in the last sample taken at the time t.

The total plasma clearance (CL_p) was calculated by the formula CL_p = dose/$AUC_{0-\infty}$; results are expressed in ml/min.

The apparent volume of distribution (V) was calculated using the formula $V = CL_p/\lambda_z$; results are expressed in l/kg.

The peritoneal clearance (CL_{PD}) was calculated by the following formula of Gibson *et al.* (1976): CL_{PD} = Q/AUC where Q is the amount of drug removed by the peritoneal dialysis within 48 h and AUC represents the area under curve during the same time interval.

The 4 h haemodialysis clearance (CL_{HD}) was calculated by the formula proposed by Bass *et al.* (1975):

$$CL_{HD} = \frac{C_A - C_V}{C_A} \cdot Q_b\ (1\text{-Ht}),$$

where C_A and C_V are respectively the plasma concentrations entering and leaving the dialyser, Q_b is the blood flow rate in the dialyser and Ht is the mean haematocrit in the samples C_A and C_V obtained at time 2.5 h.

Results

The plasma kinetics of ornidazole in the three groups of patients are illustrated in Figure 1: it can be seen that the plasma concentrations of ornidazole during haemodialysis are lower than during CAPD and that they decrease more rapidly.

The pharmacokinetic parameters of ornidazole (half-life, area under the curve from time 0 to 48 h and extrapolated to infinity, volume of distribution and clearance) in non-dialysed patients (group 1) and during CAPD (group 2) are given in tables 2 and 3. Since the half-life of ornidazole has been shown to be around 12 h, the experimentally determined area up to 48 h (AUC_{0-48}) represents 96% of the total are under the curve ($AUC_{0-\infty}$).

Parameters of peritoneal excretion are summarized in Table 4: the peritoneal clearance of ornidazole is low (3.0 ± 0.4 ml/min) and in 48 h 6.2 ± 1.1% of the injected dose can be found in the dialysis fluids.

The results obtained during haemodialysis (extraction ratio C_A–C_V/C_A, blood flow, haematocrit, 4 h haemodialysis clearance) are summarized in Table 5; elimination by haemodialysis is high: the extraction ratio through the dialyser is 42 ± 5% and the 4 h dialysis clearance is 64 ± 7 ml/min.

Discussion

The pharmacokinetics of ornidazole had already been studied in patients with normal renal function (Andersson, 1981; Richle *et al.*, 1978; Schwartz & Jeunet, 1976; Schwartz *et al.*, 1979). In these patients protein binding is less than 10% and the volume of distribution is close to 1 l/kg. Ornidazole is eliminated mainly by biotransformation. After i.v. administration,

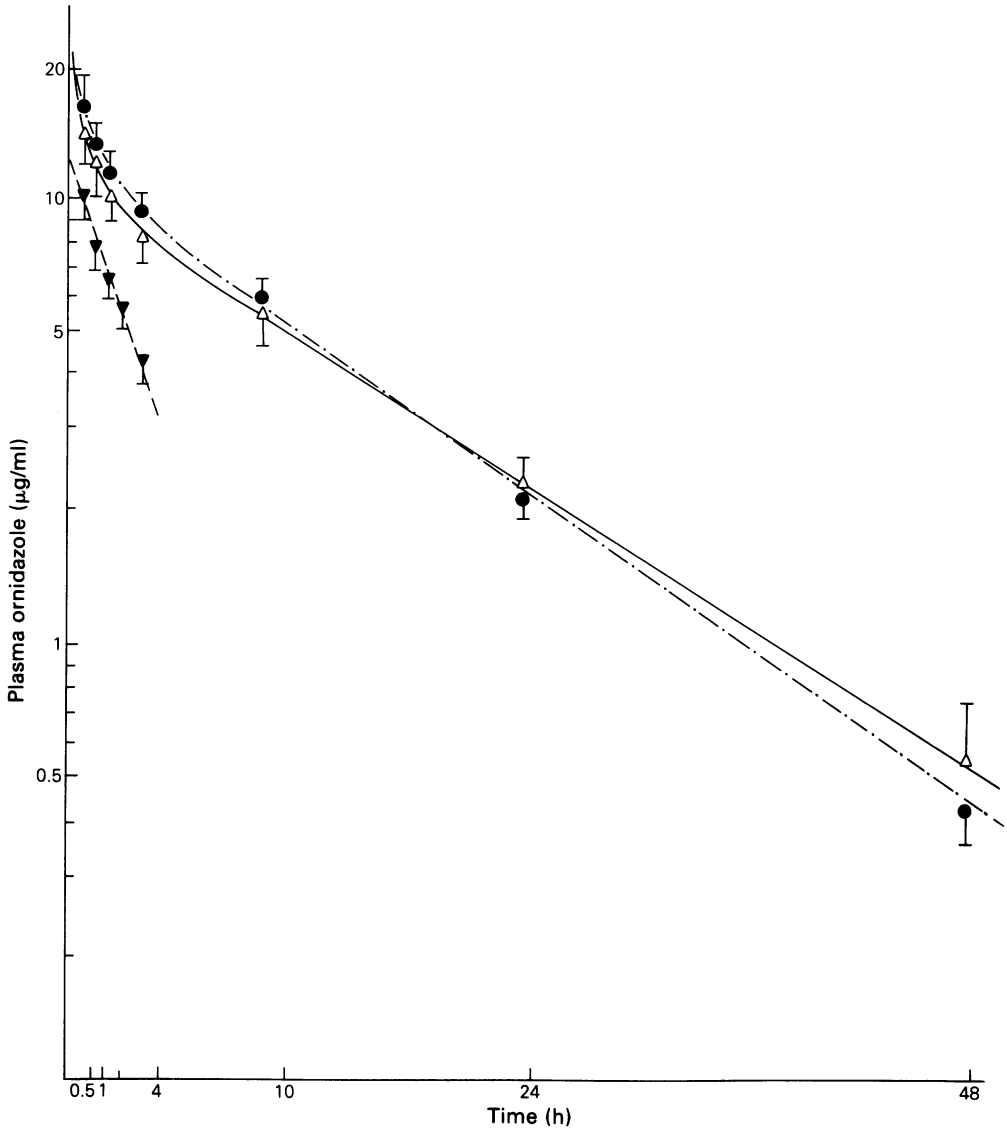

Figure 1 Mean plasma concentrations of ornidazole (± s.e. mean) after a single 500 mg intravenous dose in the three groups of patients (● group 1 without dialysis, △ group 2 CAPD and ▼ group 3 haemodialysis).

less than 5% of the dose can be found in the urine in the unchanged form. The half-life is between 11 and 13 h. Plasma and renal clearances are 90 and 5 ml/min respectively.

In patients with ACRF, total elimination of ornidazole as determined by its total plasma clearance (46.3 ± 2.6 ml/min) is lower than that calculated for patients with normal renal function (90–100 ml/min). In view of the mainly extra-renal elimination of ornidazole, one would expect an unmodified plasma clearance, as is usually the case with drugs having an extra-renal elimination (Dettli, 1974; Fabre & Balant, 1976; Singlas *et al.*, 1982; Tozer, 1974). We have no explanation for this reduction.

Nevertheless, the half-life we have reported in these patients (10.8 ± 1.4 h) remains close to that found in individuals with normal renal function. Consequently, the volume of distribution of ornidazole is smaller in the patients

Table 2 Pharmacokinetic parameters of ornidazole after a single 500 mg intravenous dose in non-dialysed patients (group 1)

Patient	$t_{1/2}$ *(h)*	AUC_{0-48} *(mg l^{-1} h)*	$AUC_{0-\infty}$ *(mg l^{-1} h)*	V *(l/kg)*	CL_p *(ml/min)*
1	10.5	151.5	157.8	0.76	52.8
2	15.1	167.6	187.0	0.72	44.6
3	11.4	177.0	186.7	0.92	44.6
4	9.4	178.1	183.6	0.88	45.4
5	8.2	240.2	244.0	0.45	34.2
6	10.3	217.0	218.6	0.55	38.1
7	8.7	140.8	143.8	0.64	58.0
8	12.6	148.3	158.7	0.88	52.5
Mean	10.8	177.5	185.0	0.73	46.3
s.e. mean	0.8	12.3	12.0	0.06	2.8

with renal failure (0.73 ± 0.06 1/kg) than in those with normal renal function (0.9–1.1 1/kg) since the volume of distribution, the half-life and the plasma clearance of a drug are linked by the formula $t_{1/2} = 0.7 \times V/CL_p$.

A reduction of the volume of distribution in renal failure has already been described for certain drugs; the reasons for such a reduction are not known (Fabre & Balant, 1976; Gibaldi, 1977; Singlas *et al.*, 1983). This reduction of the volume of distribution leads to somewhat higher concentrations than those obtained for the same dose in subjects with normal renal function (Richle *et al.*, 1978).

These results are comparable to those obtained for another nitro-imidazole derivative, metronidazole, also with mainly extra-renal elimination and a half-life which is not modified in patients with renal failure (Amon *et al.*, 1982; Cerat *et al.*, 1977).

In the course of CAPD, the pharmacokinetic parameters of ornidazole (volume of distribution, plasma clearance and half-life) are close to the ones determined in non-dialysed ACRF patients. This is due to the low peritoneal elimination of ornidazole. Only 6.2 ± 1.1% of the injected dose can be found in the dialysis fluids in 48 h. The peritoneal dialysis clearance of ornidazole is low (3.0 ± 0.4 ml/min); it amounts on an average to 60% of the peritoneal creatinine clearance (4.8 ± 0.3 ml/min). A low peritoneal elimination during CAPD has already been reported for other drugs (Golper, 1979; Maher, 1977; Singlas *et al.*, 1982; Watanabe, 1977). A review of the literature shows that the peritoneal clearance of drugs is generally low, lower than the peritoneal clearance of creatinine. Consequently their kinetics in the course of CAPD are close to that determined in non-dialysed ACRF patients with comparable renal creatinine clearance (Boutron *et al.*, 1982; Kampf *et al.*, 1980; Ruedy, 1966; Singlas *et al.*, 1983).

On the other hand, ornidazole is eliminated to a large extent by haemodialysis: the extraction ratio through the dialyser is 42.0 ± 5.0% and the 4 h dialysis clearance is 64.0 ± 7.0 ml/min, which, as for the peritoneal dialysis clearance, accounts for 60% of the creatinine clearance usually found in the course of haemodialysis with cuprophane membranes (100–120 ml/min). Low molecular weight, solubility, lack of protein binding and small volume of distribution are physicochemical and pharmacokinetic characteristics which favour elimination by haemodialysis (Gibson &

Table 3 Pharmacokinetic parameters of ornidazole after a single 500 mg intravenous dose in CAPD patients (group 2)

Patient	$t_{1/2}$ *(h)*	AUC_{0-48} *(mg l^{-1} h)*	$AUC_{0-\infty}$ *(mg l^{-1} h)*	V *(l/kg)*	CL_p *(ml/min)*
9	11.1	113.8	119.6	0.96	69.7
10	12.0	149.3	158.8	0.96	52.5
11	8.9	178.2	182.2	0.68	45.7
12	13.8	226.3	248.4	0.62	33.6
13	13.4	200.7	218.8	0.73	38.1
Mean	11.8	173.7	185.6	0.79	47.9
s.e. mean	0.9	19.6	22.5	0.07	6.3

Table 4 Peritoneal excretion (in mg and % dose) and peritoneal clearance of ornidazole in CAPD patients (group 2)

Patient	*Peritoneal excretion (mg)*	*(% dose)*	*Peritoneal clearance (ml/min)*
9	20.1	4.0	2.9
10	16.9	3.4	1.9
11	36.5	7.3	3.7
12	34.7	7.0	2.6
13	45.7	9.1	3.8
Mean	30.8	6.2	3.0
s.e. mean	5.4	1.1	0.4

Nelson, 1977; Maher, 1977; Nolph *et al.*, 1978; Watanabe, 1977). Similar results have been reported for metronidazole (Ralph, 1983).

The half-life of ornidazole during haemodialysis cannot be determined with accuracy. The duration of the dialysis session (4 h) is indeed too short compared to the half-life of the drug(11 h). Therefore it is not possible with only five samples taken at short intervals to calculate the half-life precisely. Furthermore, as the drug was injected just at the beginning of the dialysis session, the first samples were carried out partly during the distribution phase of the drug. So the initial decrease in the plasma concentrations does not reflect only the elimination but a combination of distribution and elimination. The high extraction ratio and the high dialysis clearance of the drug suggest indeed a more rapid elimination during haemodialysis than during CAPD treatment or than non dialysed treatment.

In the same manner it is not possible to calculate area under the curve and therefore to determine the volume of distribution and the plasma clearance of the drug in haemodialysed patients.

These technical difficulties are frequently observed with the drugs whose half-lives are much longer than the duration of dialysis sessions.

This study cannot provide any data about possible accumulation of metabolites in ACRF patients. Two metabolites are quantitatively the most important; one of them, [α-(chloromethyl)-2 hydroxymethyl -5 nitroimidazole -1 ethanol], results from an hydroxylation in position 2 of the imidazole ring; the other, [3-(2 methyl -5 nitroimidazole -1 yl) 1,2 propane diol], corresponds to an hydrolysis of the side chain in position 1. They account for 70% of total metabolites (Schwartz *et al.*, 1979) and they can be measured with the h.p.l.c. method used. Without antimicrobial properties and particular toxicity, they are slowly produced and normally excreted by the kidney (Richle *et al.*, 1978). However their plasma concentrations, especially after a single dose, are much lower than unchanged ornidazole concentrations and under the detection limits of the method (Merdjan *et al.*, 1983).

As far as dosage is concerned, the comparison of pharmacokinetic parameters of ornidazole in the three groups of renal insufficiency patients with the data obtained from the literature (Andersson, 1981; Richle *et al.*, 1978; Schwartz & Jeunet, 1976; Schwartz *et al.*, 1979) in normal subjects seems to indicate that there is no need to modify the dosage regimen in patients with severe renal failure, dialysed or not. The usual dosage of 500 mg every 12 h may be used. However, in haemodialysed patients, the timing of drug administration must be adapted, so that ornidazole is given at the end of dialysis and not before.

This work was supported in part by a grant of 'Fondation pour la Recherche Médicale', Paris, France.

We thank Drs Pochet and Rupin (Roche Laboratories, France) for their advice and for the supply of standards.

Table 5 Pharmacokinetic parameters of ornidazole after a single 500 mg intravenous dose in haemodialysed patients (group 3)

Patient	$\frac{C_A - C_V}{C_A}$ *(%)*	Q_b *(ml/min)*	*Ht (%)*	CL_{HD} *(ml/min)*
1	17	204	29	25
6	58	170	24	75
8	39	227	25	67
14	47	208	26	73
15	48	215	25	81
16	50	227	32	77
17	32	220	29	50
Mean	42	210	27	64
s.e. mean	5	7	1	7

References

Amon, I., Kraatz, G., Amon, K. & Peters R. (1982). Metronidazole in patients with renal insufficiency. *Drugs Under Experimental and Clinical Research*, **8**, 231–234.

Andersson, K. E. (1981). Pharmacokinetics of nitroimidazoles; spectrum of adverse reactions. *Scand. J. Infect. Dis.*, **26**, 60–67.

Bass, O. R., Nolph, K. D. & Maher, J. F. (1975). Dialysance and clearance measurements during clinical dialysis: a plea for standardization. *J. lab. clin. Med.*, **86**, 378–385.

Boutron, H. F., Brocard, J. F., Singlas, E., Charpentier, B. & Fries, D. (1982). Pharmacokinetic of furosemide in continuous ambulatory peritoneal dialysis. In *Advances in Peritoneal Dialysis. Proceedings of the second International Symposium on Peritoneal dialysis. Berlin, June 1981* Amsterdam: Excerpta Medica.

Cerat, G. A., Cerat, L. L., McHenry, M. C., Wagner, J. G., Hall, P. M. & Gavan, T. L. (1977). Metronidazole in renal failure. In *Proceedings of the International Metronidazole Conference, Montreal, May 1976*, Finegold, E. ed. pp. 404–414. Amsterdam: Excerpta Medica

Dettli, L. (1974) Elimination kinetics and dosage adjustment of drugs in patients with kidney disease. *Progress in Pharmacology*, **4**, 1–35.

Fabre, J. & Balant, L. (1976). Renal failure, drug pharmacokinetics and drug action. *Clin. Pharmacokin.*, **1**, 99–120.

Gibaldi, M. (1977). Drug distribution in renal failure *Am. J. Med.*, **62**, 471–474.

Gibson, T. P., Matusik, E., Nelson, L. D. & Briggs, W. A. (1976). Artificial kidney and clearance calculations. *Clin. Pharmac. Ther.*, **20**, 720–726.

Gibson, T. P. & Nelson, H. A. (1977). Drug kinetics and artificial kidneys. *Clin. Pharmacokin.*, **2**, 403–426.

Goldstein, E. J. C., Suttler, V. L. & Finegold, S. M. (1978). Comparative susceptibilities of anaerobic bacteria to metronidazole, ornidazole and SC-28538. *Antimicrob. Agents Chemother.*, **14**, 609–613.

Golper, T. A. (1979). Drugs and peritoneal dialysis. *Dialysis and Transplantation*, **8**, 41.43.

Jokipii, L. & Jokipii, A. M. M. (1977). Bactericidal activity of metronidazole, tinidazole and ornidazole against bacteroides fragilis *in vitro*. *J. Antimicrob. Chemother.*, **3**, 571–577.

Kampf, D., Schurig, R., Weihermüller, K. & Förster, D. (1980). Effects of impaired renal function, hemodialysis and peritoneal dialysis on the pharmacokinetics of mezlocillin. *Antimicrob. Agents Chemother.*, **18**, 81–87.

Maher, J. F. (1977). Principles of dialysis and dialysis of drugs. *Am. J. Med.*, **62**, 475–481.

Merdjan, H., Bonnat, C., Singlas, E. & Diquet, B. (1983). Measurement of ornidazole by high performance liquid chromatography. *J. Chromatogr.* **273**, 475–480.

Nolph, K. D., Popovich, R. P., Ghods, A. J. & Twardowski, Z. (1978). Determinants of low clearances of small solutes during peritoneal dialysis. *Kidney Int.*, **13**, 117–123.

Oreopoulos, D. G., Robson, M., Izatt, S., Clayton, S. & Deverer, G. A. (1978). A simple and safe technique for continuous ambulatory peritoneal dialysis. *Trans. Am. Soc. Artif. Intern. Organs.*, **24**, 484–489.

Ralph, E. D. (1983). Clinical pharmacokinetics of metronidazole. *Clin. Pharmacokin.*, **8**, 43–62.

Renaux, C., Certain, B., Mollet, M. & Rottembourg, J. (1980). La dialyse péritonéale continue ambulatoire. Le matériel et la technique. *Nouv. Presse Méd.*, **42**, 3155–3158.

Richle, R., Scholer, H. J., Angehrn, P., Fernex, M., Hummler, J., Jeunet, F., Schärer, K., Schüpbach, M. & Schwartz, D. E. (1978). Grundlagen der chemotherapie von trichomoniasis und amoebiasis mit ornidazol. *Arzneim. Forsch. Drug Res.*, **28**, 612–625.

Ruedy, J. (1966). The effects of peritoneal dialysis on the physiological disposition of oxacillin, ampicillin and tetracycline in patients with renal disease. *Can. med. Ass. J.*, **94**, 257–261.

Schwartz, D. E. & Jeunet, F. (1976). Comparative pharmacokinetic studies of ornidazole and metronidazole in man. *Chemotherapy*, **22**, 19–29.

Schwartz, D. E., Jordan, J. C., Vetter, W. & Oesterhelt, G. (1979). Metabolic studies of ornidazole in the rat, in the dog and in man. *Xenobiotica*, **9**, 571–581.

Singlas, E., Colin, J. N., Rottembourg, J., Meessen, J. P., De Martin, A., Legrain, M. & Simon, P. (1982). Pharmacokinetics of sulfamethoxazole-trimethroprim combination during chronic peritoneal dialysis; effect of peritonitis. *Eur. J. clin. Pharmac.*, **21**, 409–416.

Singlas, E., Boutron, H. F., Merdjan, H., Brocard, J. F., Pocheville, M. & Fries D. (1983). Moxalactam pharmacokinetics during chronic ambulatory peritoneal dialysis. *Clin. Pharmac. Ther.*, **3**, 403–407.

Tozer, Th. N. (1974). Nomogram for modification of dosage regimens in patients with chronic renal function impairment. *J. Pharmacokin. Biopharm.*, **2**, 13–28.

Watanabe, A. S. (1977). Pharmacokinetics aspects of dialysis of drugs. *Drug Intell. Clin. Pharmac.*, **11**, 407–416.

Winchester, J. F., Gelfand, M. C. & Knepshield, J. H. (1977). Dialysis and hemoperfusion of poisons and drugs. *Trans. Am. Soc. Artif. Intern. Organs.*, **23**, 762–770.

(Received April 3, 1984, accepted October 10, 1984)